



LABORATORIES PLC

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14 March 2000

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fisher Lane, Room 1061
Rockville, MD 20852 USA

Dear Sir or Madam:

Re: Docket No. 99D-5199

Comments On FDA Draft Guidance Document: "Guidance for Resorbable Adhesion Barrier Devices for Use in Abdominal and/or Pelvic Surgery" - released for comment on 16 December 1999.

ML Laboratories PLC is a member of "The Industry Adhesion Barrier Task Force" which was established to provide a combined industry response to the above guidance document.

The company is fully supportive of the comments which have been submitted by the representative of this Task Force - James W Burns. In addition, we would like to elaborate on the following points:

1. Preclinical Data - Section V Manufacturing

B. Final Product Specification

The guidance document provides examples of tests which can be included on the final product release specification. This list includes a test for "levels of adhesion reduction in an animal model". However, a test for physico/chemical characterisation of the product has not been listed.

We consider that if a product can be characterised by physico/chemical means for its major component and impurities, then a biological assay would be redundant. Chemical assays are recognised to be more reproducible than biological assays and would always be the method of choice.

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It is accepted that not all products can be characterised by physico/chemical methods and that, in this situation, an alternative method for checking the levels of the product's constituents would be required. A biological assay may be the only option available for this, but we consider that an *in vitro* assay should be used rather than the *in vivo* test in an animal model, as suggested by the guideline.

The ability of a product to perform as intended (reduce/prevent adhesions) is established during the development programme which addresses the product design, formulation constituents, manufacturing process, finished product release specification and stability, together with preclinical and clinical testing for safety and efficacy. The finished product release specification is modified and adapted during the development phase to establish a set of tests which guarantee the reproducibility of a product on a batch to batch basis.

Thus, if the reproducibility of the product is ensured, there is no reason to expect its intended performance to vary by batch.

We consider, therefore, that a biological assay should only be required for release testing of those products that cannot be characterised by physico/chemical means and that this should be an *in vitro* rather than *in vivo* test, to avoid an unnecessary use of experimental animals.

The guidance document should include a test for chemical characterisation in its list of examples of final product release specifications. The *in vivo* biological test should be replaced by an *in vitro* test.

C. Product Expiration Dating

The guidance document recommends that the incidence of *in vivo* adhesion reduction should be measured during stability studies, as for the finished product release specification.

As discussed above, we do not consider that a biological assay should be required for a product which can be characterised by physico/chemical means. Chemical assays provide more robust stability data than biological assays, from which stability data are difficult to interpret, due to the inherently large variability in the results obtained.

If the product cannot be characterised by physico/chemical means and is being analysed by an *in vitro* biological method for product release, then this is the method that should be used during the stability studies.

We consider that the requirement for *in vivo* testing for incidence of adhesion reduction should be deleted from this section of the guidance document.

2. Clinical Investigational Plan - Pre-market and post approval data requirements versus indications for use

The guidance document suggests that post marketing studies, to assess clinical outcomes which have not been stated in the indications for use, may be required as a condition of approval.

We are surprised that FDA can request such studies. We consider that the sponsor should be able to restrict the indications for use (label claim) to the clinical endpoint that has been assessed in the pre-market studies (such as reduction/prevention of adhesions). It should then be the sponsor's prerogative to perform clinical outcome studies if the company wishes to extend the label claim.

Please do not hesitate to contact me if you wish to discuss any of the above comments.

Yours faithfully

A handwritten signature in cursive script, reading "Lorna M. Clisby".

Mrs Lorna M Clisby
Director of Regulatory Affairs



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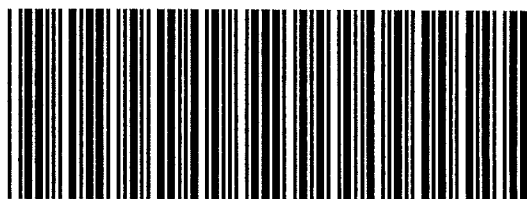
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